CYCLIC BIS-COMPOUNDS CLEARING MALFORMED PROTEINS

ABSTRACT

[00204] The invention is drawn to compositions and methods for inhibiting and treating malformed forms of proteins causing neurodegenerative disease, such as protease resistant prion proteins (PrP^{Sc}) and those associated with transmissible spongiform encephalopathies (TSEs). Bis-acridines are characterized by a dimeric motif, comprising two acridine heterocycles tethered by a linker. A library of bis-(6-chloro-2-methoxy-acridin-9-yl) and bis-(7-chloro-2-methoxy-benzo[*b*][1,5]naphthyridin-10-yl) analogs were synthesized to explore the effect of structurally diverse linkers on PrP^{Sc} replication in ScN2a cells. Structure-activity analysis revealed that linker length and structure effect inhibition of prion replication in cultured, scrapied cells. Three bis-acridine analogs, (6-chloro-2-methoxy-acridin-9-yl)-(3-{4-[3-(6-chloro-2-methoxy-acridin-9-ylamino)-propyl]-piperazin-1-yl}-propyl)-amine, *N,N'*-bis-(6-chloro-2-methoxy-acridin-9-yl)-1,8-diamino-3,6-dioxaoctane, and (1-{[4-(6-chloro-2-methoxy-acridin-9-ylamino)-butyl]-[3-(6-chloro-2-methoxy-acridin-9-ylamino)-propyl]-carbamoyl}-ethyl)-carbamic acid *tert*-butyl ester, showed half-maximal inhibition of PrP^{Sc} formation at effective concentrations (EC_{50}) of 40 nM, 25 nM and 30 nM, respectively, and were not cytotoxic for uninfected neuroblastoma cells at concentrations of 500 nM. The data produced here shows that bis-acridine analogs prevent or slow PrP^{Sc} replication.